Fezolinetant for treating vasomotor symptoms associated with the menopause

For screen – contains redacted information

Technology appraisal committee C [06 Jan 2025]

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Company: Astellas Pharma Ltd

Fezolinetant for treating vasomotor symptoms associated with the menopause

- ✓ **Background, responses to draft guidance and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations

NICE National Institute for Health and Care Excellence

Conclusions at ACM1

Committee recommendation

- Fezolinetant should not be used to treat moderate to severe vasomotor symptoms caused by menopause

Committee preferred assumptions

- Positioning: Secondary care might be more appropriate than primary care
- Comparators: non-hormonal treatments (primary care), no pharmacological treatment (secondary care)

Committee requested analysis

- Costs and other implications of secondary care prescribing
- Including all relevant comparators
- Explore other approaches to utility values
- NMA evidence for all treatments used in the NHS and using relative treatment effects in model
- Updated model structure

Committee identified uncertainties

- the setting in which fezolinetant (FEZO) would be prescribed
- generalisability concerns, limited effectiveness evidence for people with <7 VMS who can't have HRT
- model structure didn't capture the full impact of VMS, or treatment effect on VMS
- model didn't include a relative comparison against placebo and used natural history* estimates based on clinical opinion → robust comparison not possible
- approach of adjusting utility values based on clinical opinion was inappropriate
- uncaptured costs, including the costs for additional liver monitoring

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Abbreviations: FEZO, fezolinetant; HRT, hormone replacement therapy; VMS, vasomotor symptoms

*natural progression of VMS from diagnosis through to latest stage

Fezolinetant (Veoza, Astellas Pharma Ltd)

Marketing authorisation	Moderate to severe* vasomotor symptoms associated with menopause. Granted December 2023 (MHRA)
Contraindication and monitoring	• Not recommended for people with liver disease** or undergoing oncologic treatment for breast cancer or other oestrogen-dependent malignancies as the safety and efficacy are unknown. • Women with previous breast cancer or other oestrogen-dependent malignancies and no longer on any oncologic treatment have not been included in the clinical studies. A decision to treat should be based on a benefit-risk consideration for the individual. • Further to the SmPC, MHRA and company have agreed that liver function tests prior to treatment are needed, monthly for the first 3 months and periodically thereafter based on clinical judgment.
Administration	Oral (45 mg daily)
Price	• £44.80 per 28 tablet pack • £584.40 per person each year

Abbreviations: EMA, European medicines agency; FDA, food and drug agency; MHRA, Medicines and Healthcare products Regulatory Agency; SmPC summary of product characteristics.
** Specifically Child-Pugh Class B (moderate) or C (severe) chronic hepatic impairment

*EMA/FDA definitions of vasomotor symptoms used in trial:
- Moderate: sensation of heat with sweating, can continue activity
- Severe: sensation of heat with sweating, can't continue activity

Equality considerations

At ACM1

Committee noted importance of considering these in this appraisal

- Unmet need reflects historical lack of innovation in menopause and women's health.
- Younger people affected by premature or induced menopause and abrupt onset VMS
- VMS more prevalent, greater severity/duration in Black and Hispanic people
- Black African and Caribbean people may be less likely to choose HRT.
- Some groups experience menopause earlier; have higher hysterectomy rates; have different cultural values and views on menopause; may have less access to treatment
- Higher impact and prevalence of VMS noted to reflect type of work and education
- Transgender and non-binary people: Access to appropriate care might be more difficult

Consultation comments

- BMS and SfE: without NICE approval, new treatment only available privately to those who can afford it, furthering health inequalities. Current system favours socially/economically advantaged people
- By prioritising HRT and offering CBT as an alternative without considering accessibility, guidelines risk creating a two-tier care level, causing socioeconomic discrimination
- SfE: some groups underrepresented in research on treatments for menopause and VMS
  - E,g., no high-quality data for HRT safety in some people from ethnic minority backgrounds
- People with cancer diagnosis protected by equalities act (under disability) and should be prioritised
- People may choose not to use hormone-based treatments based on religion

Abbreviations: BMS, British Menopause Society; CBT, cognitive behavioural therapy; HRT, hormone replacement therapy; SfE, Society for Endocrinology; VMS, vasomotor symptoms.

Consultation responses – professional organisations

British Menopause Society

Modelling

- Possible duration of having VMS should be considered – can last >10 years (Avis,2015)

Population

- Clinical benefit uncertain and increased cost associated with LFTs doesn't warrant use in all women with VMS at present.
- Populations that are most likely to benefit not addressed in this appraisal (people with breast cancer or have had hormone sensitive cancer)
- Menopause specialists are getting good results using FEZO off-license in people who have had breast cancer and are on endocrine treatment (endocrine treatment can make VMS worse, and people may stop this recurrence preventative treatment because of exacerbated symptoms)
- Recommending this for this sub-group of people would provide an invaluable treatment option for vulnerable people currently excluded from adequate menopause support

Abbreviations: BMS, British Menopause Society; FEZO, fezolinetant; HRT, hormone replacement therapy; LFT, liver function test; VMS, vasomotor symptoms.

References: Avis, N. E., (2015). "Duration of menopausal vasomotor symptoms over the menopause transition." JAMA Intern Med 175(4): 531-539

Consultation responses – professional organisations

Society for Endocrinology

Generalisability to NHS practice

- The duration of treatment trajectories within the NICE appraisal may be overestimated

Current treatment

- No effective treatment option for when HRT is unsuitable, risk of using HRT treatment by default anyway
- Anti-depressants do not address the underlying cause of menopause symptoms directly and many women find they are ineffective, have intolerable side effects or are averse to their use

Primary care setting

- Common practice measuring LFTs in primary care but more information needed on the relevance and frequency of liver disease with FEZO use in NHS population to understand impact
- Some people with more complex cases will already be being seen in secondary care

Abbreviations: HRT, hormone replacement therapy; LFT, liver function test; SfE, Society for Endocrinology;

Consultation responses – web comments summary

Major unmet need for treatment alternatives for people who can't have HRT

- A total of 84 comments were received in response to the draft guidance

Living with vasomotor symptoms

- Impact on CVD risk associated with unmanaged VMS, ability to work, exercise, sleep (examples include sleeping for 1 or 2 hours per night), brain fog, anxiety, fatigue, relationships, depression

Current appraisal

- People who either can't or choose not to use HRT have not been considered when reviewing treatment options

Fezolinetant benefits

- Responses express positive impact observed in practice; productivity, improved life, ability to resume participation in society and care for dependents many responses saying they work well to reduce hot flushes
- For >60 years, HRTs benefits often don't outweigh the risks, FEZO would benefit this population and this may not be reflected in trial (only to 65 years)
- Even if only recommended to a small group of people, having an choice or alternative treatment is important in a field that has very few options

Abbreviations: CVD, cardiovascular disease; FEZO, fezolinetant; HRT, hormone replacement therapy; VMS, vasomotor symptoms

Consultation responses – web comments summary

Current treatment

- The population currently treated with unlicenced alternatives with significant side-effect profiles
- SSRIs and SNRIs have many negative side-effects, these were not considered when considering the perceived lack of benefit of FEZO (see model parameters)
- CBT impossible to access, insulting to suggest CBT in management of debilitating hot flushes and night sweats
- Without a licenced and regulated treatment, people will often look to manage symptoms themselves which can potentially cause harm

Other research

- Meta-analysis by Morga et al that demonstrates the benefit of FEZO over SSRIs/gabapentin

Concerns with FEZO

- Neoplasm and liver function concerns; unknown risk of long-term blocking of neurokinin receptors and people need to know the FEZO blocks protein that reduces metastatic spread of cancer; long term studies on this impact needed

Abbreviations: CBT, cognitive behavioural therapy; FEZO, fezolinetant; HRT, hormone replacement therapy; NG, NICE guideline; NMA, network meta-analysis; SNRI, Serotonin-norepinephrine reuptake inhibitors; SSRI, Selective serotonin reuptake inhibitor, VMS, vasomotor symptoms

Key issues: Clinical effectiveness

	Conclusion at ACM1	Company response	EAG response
Prescribing setting	Secondary care may be more appropriate	Primary care	EAGs CE suggests either but expect FEZO to be initiated in primary care
Population	FEZO considered for people with moderate to severe VMA, for whom HRT is unsuitable	-	-
Comparators	If primary care → non-hormonal treatments that are offered in primary care If secondary care → later option in pathway so, no 'pharmacological treatment' may be most appropriate	No active treatment most relevant comparator	No treatment may be relevant for some but non-hormonal pharmacological treatments likely the most appropriate comparator. Company's prescribing setting and comparators contradict committees' conclusions at ACM1
Generalisability	Results may not be generalisable to population eligible, particularly people with < 7 VMS /day	Restricted to ≥7 VMS /day by FDA	Concerned how people with <7 VMS /day may not have as big a treatment effect

Abbreviations: CE, clinical expert; FDA, food and drug agency; FEZO, fezolinetant; HRT, hormone replacement therapy; SNRI, Serotonin-norepinephrine reuptake inhibitors; SSRI, Selective serotonin reuptake inhibitor, VMS, vasomotor symptoms

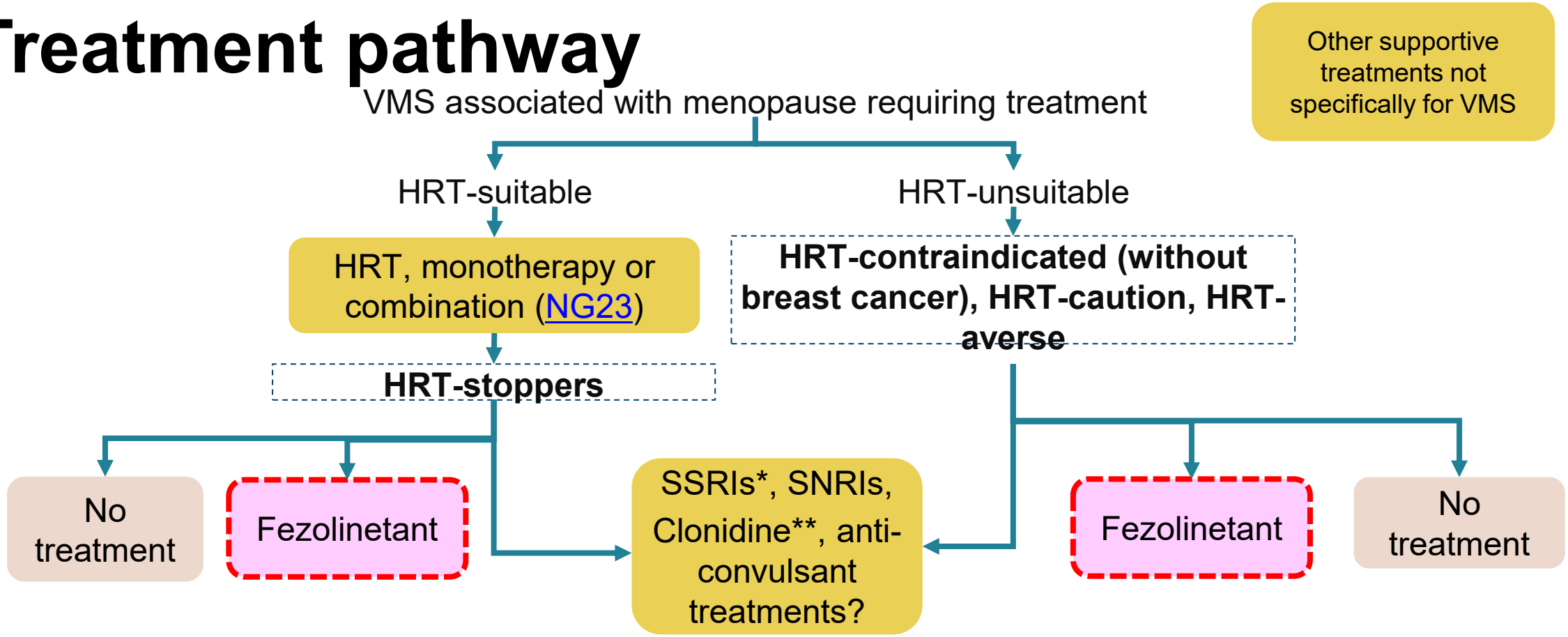
Key issues: Cost effectiveness

New model solves issues from ACM1 but introduces areas of uncertainty in utilities

	Conclusion at ACM1	Company response	EAG response	ICER impact
New modelling approach + utilities	-	• Updated response based model structure	• Misalignment in model structure for AT vs NAT arm → only AT arm includes partial responders • Remove 52 week stopping rule, for partial responders	Small
Treatment dependent utility values	-	• Treatment dependent utility values for responders and partial responders	• Treatment independent utilities for desvenlafaxine and paroxetine arm	Medium
Uncaptured costs of liver monitoring	Liver monitoring to be included as specified in the MA	• Included liver monitoring costs	• Includes: liver monitoring costs + costs of nurse appointment and annual LFT	Small
Incorporation of VMS severity	By not incorporating VMS severity, model may not be fully capturing the benefits of FEZO	• New response-based model structure • Scenario analysis using patient perspective tool PGI-C for VMS • VMS severity captured to some extent in trial (see moderate-severe classifications)	• New model structure solves some issues • VMS severity may still not be fully captured	Unknown

Abbreviations: AT, active treatment; DESV, desvenlafaxine; FEZO, fezolinetant; ICER, incremental cost-effectiveness ratio, MA, marketing authroisation; NAT, non active treatment PARX, paroxetine; VMS, vasomotor symptoms; PGI-C, the Patient Global Impressions Scale - Clinical for VMS

Treatment pathway



*Recommended for those with breast cancer not taking tamoxifen (NG101)

Web responses**

Clonidine: only licenced non-hormonal treatment. However, NAMS actually advises against clonidine. BMS has cited NAMS as recommending clonidine.

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Abbreviations: HRT, hormone-replacement therapy; NAMS, North American Menopause Society; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; VMS, vasomotor symptoms

Key issues: Prescribing setting for fezolinetant (i)

There is uncertainty around where fezolinetant would be best prescribed

AT ACM1

- Clinical experts: Not concerned about managing liver risks but would be a large impact of additional appointments/costs in primary care. So, secondary care may be more appropriate
- Committee: secondary care might be more appropriate

Professional organisation perspectives

- Common practice measuring LFTs in primary care with medications such as statins and ACE inhibitors
- Information needed on nature of liver disease e.g., comparison frequency/incidence in NHS population
- Many HRT-unsuitable women have complex underlying health issues and could be initiated in specialist women's health or secondary care settings, with subsequent prescribing and review in primary care.

Web responses

- FDA warning is important - regular monitoring of liver function is needed.

FEZO should be prescribed in primary care

- Many medications already require these tests; some of population may be having tests already
- Long waiting lists and demand on services, restricting to secondary care may introduce regional disparities in access to FEZO

FEZO should be prescribed in secondary care

- If all other treatment options are exhausted people should be referred to secondary care
- LFTs introduce extra burden and costs for GPs
- Secondary care or special interest GPs may be a more appropriate setting

Abbreviations: FEZO, fezolinetant; HRT, hormone replacement therapy; LFTs, liver function tests; VMS, vasomotor symptoms

Related key issue: liver monitoring costs

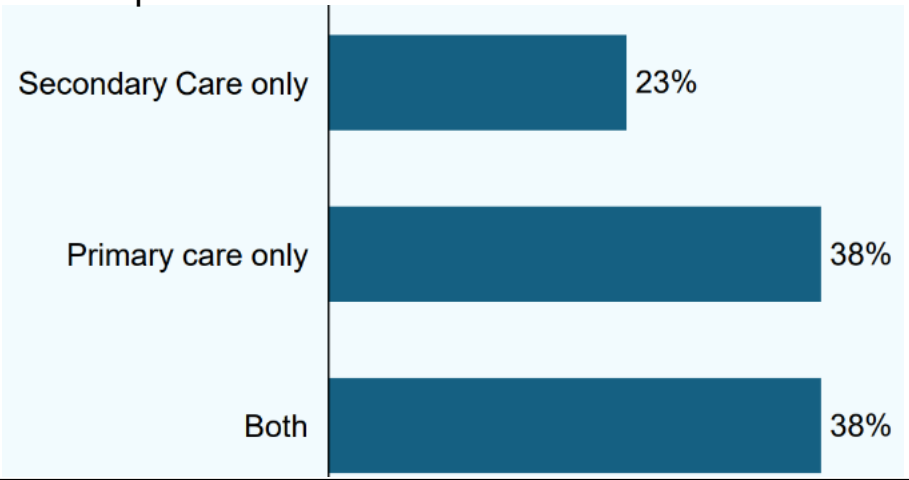
Key issues: Prescribing setting for fezolinetant (ii)

There is uncertainty around where fezolinetant would be prescribed

Company

- Positioned FEZO to be prescribed in primary care, clinical experts state LFTs are already routine
- Access through secondary care limited due to waiting lists, FEZO in primary care will help to improve access and disparities in care + small population eligible unlikely to have impact according to BIA
- For secondary care median waiting time: 6 months

GP omnibus survey results when asked by where FEZO should be prescribed



EAG :

- Most GPs very (35%) or moderately (46%) confident making clinical decisions based on liver test results
- Clinical expert: FEZO could be used in either but expect FEZO to be initiated in primary care

NICE:

- NICE's role: to ensure cost-effectiveness is accurately estimated for the setting that fezolinetant will be used
- May also be important to consider the impact of a recommendation in each setting on how far each setting will address some of the health inequalities raised

In which setting should fezolinetant be modelled?

Related key issue: liver monitoring costs

NICE

Abbreviations: BIA, budget impact analysis; FEZO, fezolinetant; HRT, hormone replacement therapy; LFTs, liver function tests; VMS, vasomotor symptoms

Key issues: Comparators

What are the appropriate comparators?

ICER Impact: Large

AT ACM1

- If primary care → non-hormonal treatments that are offered in primary care (e.g SSRI/SNRI)
- If secondary care → later option in pathway so, no 'pharmacological treatment' may be most appropriate

In primary care the comparator/s are:

No active treatment (company and web responses)

Company

- No active treatment most relevant comparator for FEZO as it is the clinical reality of most patients
- Responder model doesn't support inclusion of most other comparators (see NMA section)

Web responses

- Too much emphasis on SSRIs: prescribed as no other option: many people on SSRI/SNRIs describe symptoms as severe/unbearable (Kantar insights, 2022)
- If secondary care → should not be alongside or as an alternative to non-hormonal treatments

Non-hormonal treatments and no treatment (EAG)

EAG comments

- Company's GP survey suggest that SS/SNRIs is more likely than no treatment (on next slide)
- UK study (n = 1195; Glynne, 2025) 46% have antidepressants for menopausal symptoms
- EAG clinical expert: clonidine less effective than SS/SNRIs but reluctant to prescribe some anticonvulsants due to AEs
- No treatment relevant for some but, non-hormonal pharmacological treatments = most relevant comparator
- Non-hormonal treatments should be considered as a comparator

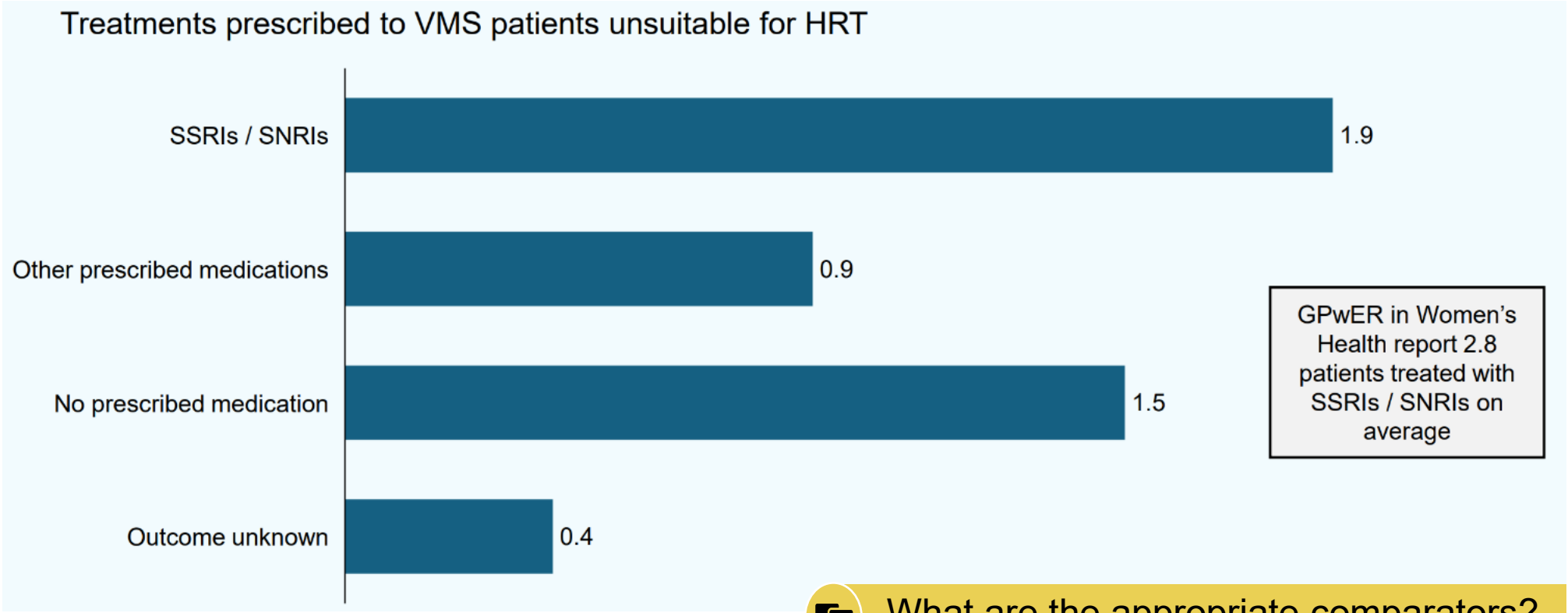
Abbreviations: HRT, hormone replacement therapy; FEZO, fezolinetant; NAMS, North American menopause society; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; VMS, vasomotor symptoms

GP Omnibus survey - Comparators

Q3. Approx. how many people consult with you about moderate to severe VMS in a three-month period → 15.4

Q6. Of those people (Q3) how many are unsuitable for HRT → medical reasons= 2.4; individual aversion= 2.2

Q7. Of those people (Q6), how many are prescribed the following non-hormonal pharmacological treatments for VMS:



What are the appropriate comparators?

NICE

Abbreviations: HRT, hormone-replacement therapy; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; VMS, vasomotor symptoms

Fezolinetant for treating vasomotor symptoms associated with the menopause (2)

- ❑ Background, responses to draft guidance and key issues
- ✓ **Clinical effectiveness**
- ❑ Modelling and cost effectiveness
- ❑ Other considerations

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ICER Impact: Unknown

Key issues: Generalisability to the NHS population

At ACM1

- People with <7 VMS /day in NHS, but not covered by trial. Generalisability risk

Company response to draft guidance

- ≥7 moderate to severe* VMS was eligibility mandate by FDA for trial (EMA is ≥ 5)
- Experts suggest people who seek treatment likely to be people with >7 VMS /day

*EMA/FDA definitions used in trial:

- Moderate: sensation of heat with sweating, can continue activity
- Severe: sensation of heat with sweating, can't continue activity

EAG comments

- Around 20% of screened patients for FEZO trials were excluded because they had <7 VMS events per day
- Company experts also said they wouldn't just rely on frequency and would use QoL to assess treatment need
- FEZO may not be as effective in NHS population, given significantly smaller treatment effect seen in 'below median' (median,9.78) VMS frequency subgroup (MD -1.36) compared with 'above median' subgroup (MD -3.66)
- Concerning that company did not investigate whether a similar effect was seen in DAYLIGHT
- Plausible that it might be more difficult to achieve a 50% reduction from 4 to 2 events than from 8 to 4
- Efficacy of FEZO remains uncertain for those with chronic diseases or high blood pressure (low numbers in trials)
- Clinical trial evidence is post-menopausal whereas MA population is peri and post-menopausal

Web responses

- FEZO would be effective in people with <7 VMS per day with equally mod/severe symptoms, based on MOA
- Populations likely to benefit not addressed (people with breast cancer or have had hormone sensitive cancer)

How generalisable is the clinical evidence to NHS practice?

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Abbreviations: EMA, European Medicines Agency; FDA, food and drug agency; HRT, hormone replacement therapy; MOA, mode of action; MD, mean difference, SNRI, Serotonin-norepinephrine reuptake inhibitors; SSRI, Selective serotonin reuptake inhibitor, VMS, vasomotor symptoms

Network Meta-analysis summary

*See appendix for NMA detail

Company provided some NMAs in response to committee request

- Company provided NMAs with some non-hormonal pharmacological treatments in response to DG request
- 13 trials identified; 5 for the treatment response NMA, 8 for the discontinuation NMA
- NMA comparisons versus desvenlafaxine conducted for response and discontinuation rates
    - A response was defined by ≥75% reduction in moderate to severe VMS frequency at week 12 from baseline
- NMA comparison versus paroxetine conducted for discontinuation
    - Paroxetine was not included as a comparator for responses as no data was available for the relevant response definition (≥75% reduction from baseline). Response definition for paroxetine was 50% VMS frequency reduction at week 12 from baseline). Company note that 7.5mg is lower than the dose used in the UK of 10-20mg.
- Company submitted combinations of
    - Simple (doses analysed separately) and exchangeable class effect (single estimate for all doses) NMAs
    - Fixed and random effects models
    - Primary (only 50mg and 100mg desvenlafaxine included in network) and sensitivity (all doses of desvenlafaxine included in network) NMAs

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Abbreviations: NMA, network meta-analysis

Network Meta-analysis summary

Differences in NMA preferences and opinions between company and EAG

NMA Parameter	Company	EAG
Choice of SNRI	Use 100mg desvenlafaxine as proxy for NHS used venlafaxine	Agree this is appropriate proxy
Gabapentin	Not included in NMA because BREEZE 1-3 trials had doses higher than BMS recommended 900mg/day	BREEZE doses (1200-1800mg/day) lower than maximum UK licensed dose (3600mg). Unclear why excluded. Also note paroxetine included despite dose mismatch (7.5mg) to NHS (10-20mg).
Simple NMA vs Class models	Prefer simple NMA (single doses of treatments compared)	Agrees with this preference
Analysis used	Base case: restricted dose NMA for desvenlafaxine	Sensitivity analysis: extended dose NMA – because additional evidence in network can more reliably estimate between-study heterogeneity → reduces uncertainty in results
NMA model	Random effects for response Fixed effects for discontinuation	Random effects for both outcomes
Missing data	Use last observation carried forward	Only viable option available to company given comparator trial methods → reasonable approach

Abbreviations: NMA, network meta-analysis

NMA results summary

Appendix: Key trial results by response definition

NMA results include possibility of no treatment effect comparing FEZO and DESV but lower discontinuation for FEZO than DESV and PARX

Response NMA analysis (Response is ≥75% reduction from baseline at week 12)	**OR placebo vs FEZO (95% CrI)**	**OR DESV vs FEZO (95% CrI)**	**OR PARX vs FEZO (95% CrI*)**
Simple NMA – Random effects base case **(Company)**	0.39 (0.19 to 0.84)	0.84 (0.36 to 2.09)	Not conducted**
Simple NMA – Random effects – sensitivity analysis **(EAG)**	0.39 (0.22 to 0.70)	0.84 (0.42 to 1.73)	Not conducted**
Discontinuation NMA analysis (at week 12)	**OR placebo vs FEZO (95% CrI)**	**OR DESV vs FEZO (95% CrI)**	**OR PARX vs FEZO (95% CrI)**
Simple NMA – Fixed effects base case **(Company)**	[redacted]	[redacted]	[redacted]
Simple NMA – Random effects – sensitivity analysis **(EAG)**	[redacted]	[redacted]	[redacted]

* Not all results shown, only base cases. Please see company DG response Tables 6 to 10 for full results

** Company did not include PARX in the response NMA as no 75% reduction outcome available

Abbreviations: DESV, desvenlafaxine; FEZO, fezolinetant; NMA, network meta-analysis; PARX, paroxetine

Fezolinetant for treating vasomotor symptoms associated with the menopause (3)

- ❑ Background, responses to draft guidance and key issues
- ❑ Clinical effectiveness
- ✓ **Modelling and cost effectiveness**
- ❑ Other considerations

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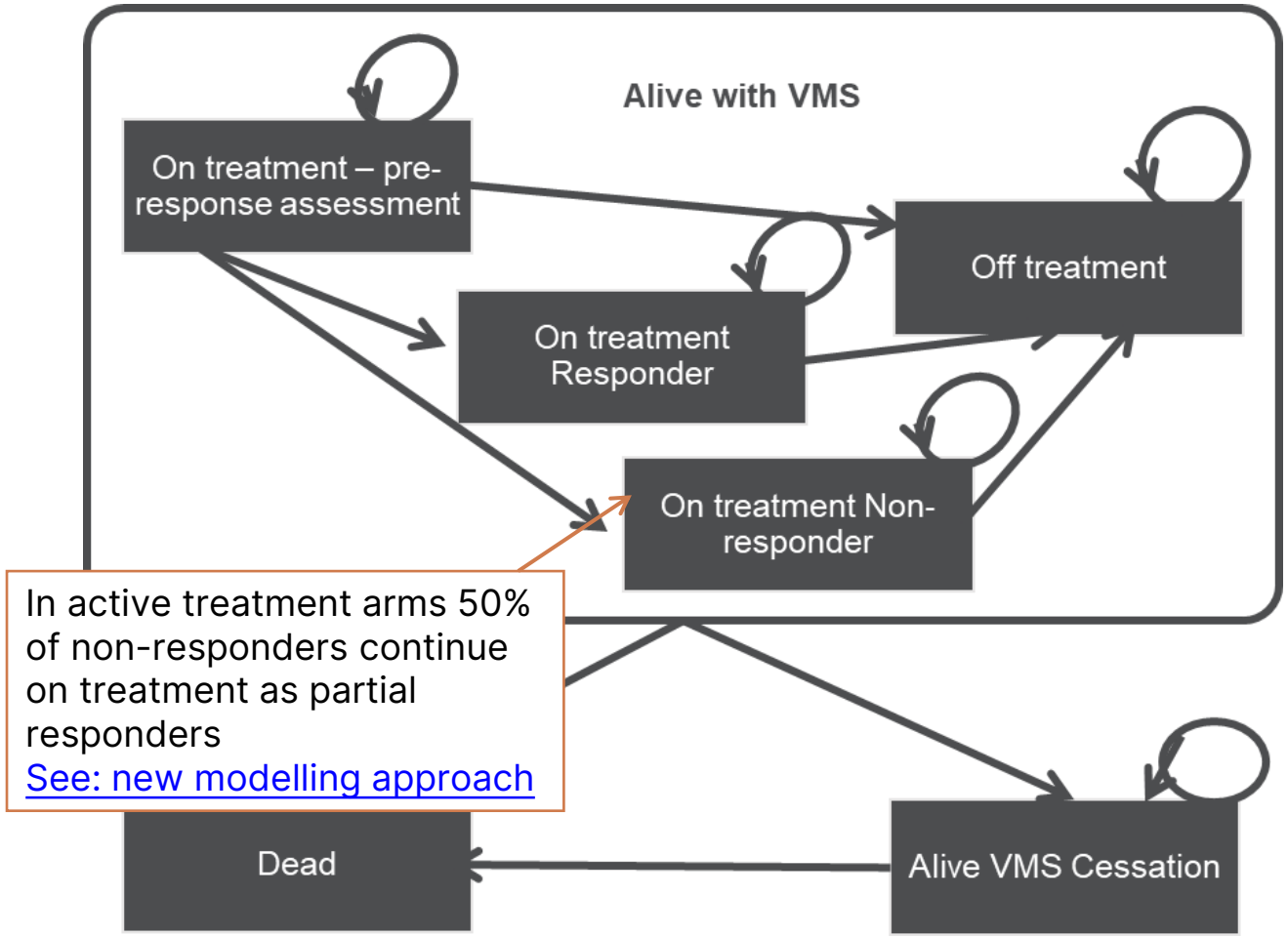
Company's model overview

New response-based model compares FEZO with no active treatment and DESV/PARX. Includes natural cessation of VMS. 10-year time horizon, 4-week cycle length



- Modelled cohort average age 51 and post menopausal
- Start in 'on treatment-pre-response' to wk 12
- Move to 'responder': ≥75% VMS reduction*
- Move to 'off treatment': <50% reduction*

Only in AT arm

- Move to 'on treatment non-responder': considered partial responders: ≥ 50% but <75% VMS reduction*)

What committee concerns does this address?

- Includes relative treatment effects
- Removes VMS frequency health states and need to define a baseline for these states
- Uses trial data instead of natural history
- Accounts for placebo effect in both arms

Abbreviations: AT, active treatment arms; DESV, desvenlafaxine; FEZO, fezolinetant; PARX, paroxetine VMS, vasomotor symptoms. *reduction of moderate to severe VMS frequency at week 12 from baseline

Informing the cost-effectiveness model

Model parameter	Evidence source	Notes
Response* in FEZO and “no active treatment” arms	Pooled DAYLIGHT and SKYLIGHT 1&2 12 week assessment	Scenarios explore different response definitions
Response* in DESV arm	OR from NMA applied to FEZO arm	From 5 studies in the NMA
Partial response in FEZO / DESV arms (≥50% to <75% reduction from baseline)	Half of people that didn’t reach a 75% reduction are partial responders. Company: reflects partial responders in DAYLIGHT/SKYLIGHT 1&2, and clinical opinion.	All partial responders stop treatment at Week 52. EAG scenario removes this stopping rule.
Response in the PARX arm (50% reduction from baseline)	Weighted average absolute response data from NCT01361308/NCT01101841	In this scenario FEZO response also set to 50% reduction.
Transition to VMS cessation	>50% transition to VMS cessation by ~5 years	Independent of treatment or health state
Transitions to death	Mortality = general population	
Discontinuation in FEZO and placebo arm	Pooled DAYLIGHT and SKYLIGHT 1&2 12 week assessment	Health state, treatment and timepoint specific
Discontinuation in DESV and PARX arms	From discontinuation NMAs	Health state, treatment and timepoint specific
Safety	FEZO – DAYLIGHT DESV - Bouchard et al	SSRIs and SNRIs may be conservative: full range of AEs may not be captured

Abbreviations: DESV, desvenlafaxine; FEZO, fezolinetant; NMA, network meta-analysis; PARX, paroxetine * ≥75% reduction of moderate to severe VMS frequency from baseline

Key issues: New modelling approach for health states & utilities

At ACM1

- Issues with the company modelling approach, led company to produce an updated model structure for ACM2

Company response to draft guidance

- With new model structure health states and utilities are now defined based on a percentage (75% in base case) reduction in moderate to severe VMS frequency at Week 12 (aligns with NG23) from baseline

Web responses

- Responses differed: some see frequency as a key measure of impact and a measure of severity; others see severity and frequency as two separate drivers of impact.

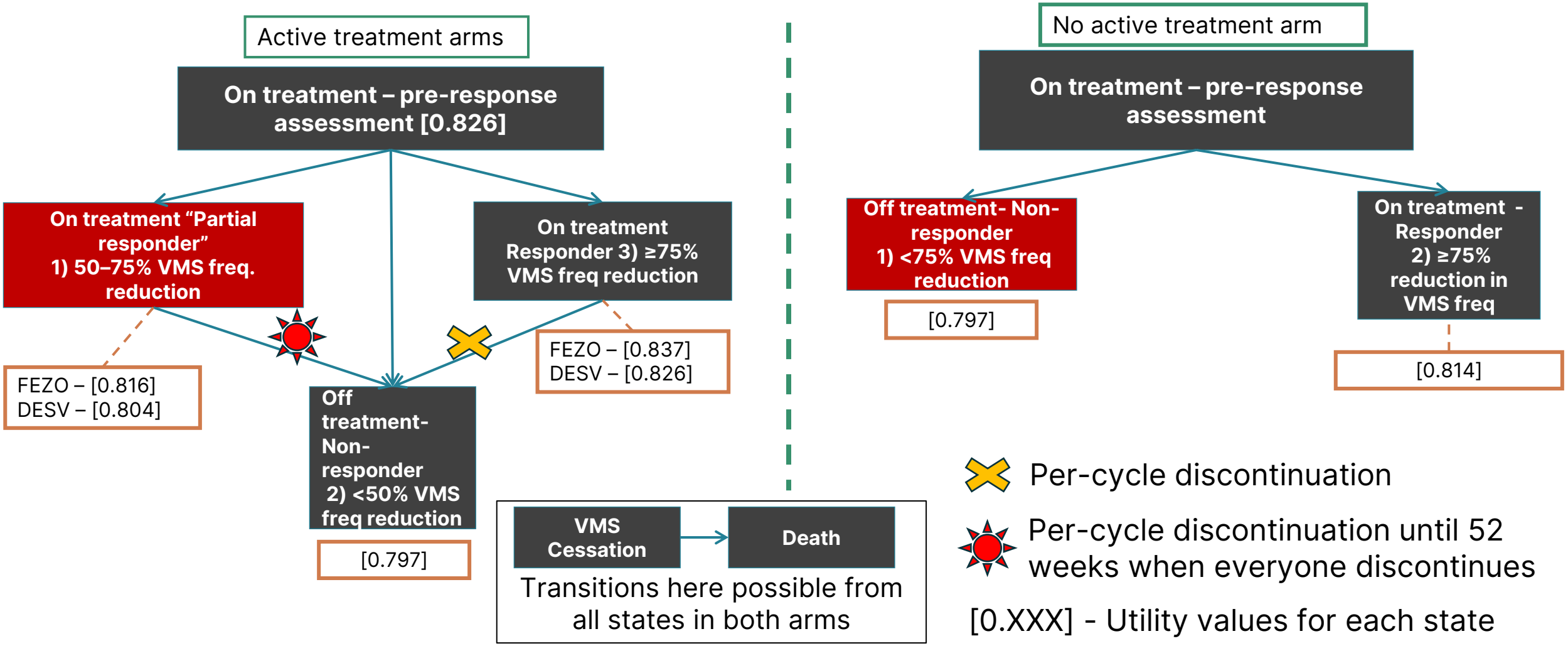
EAG comments (see next slide for visual summary)

- 12-weeks appropriate as aligns with 3 months in NG23 to assess efficacy and tolerability of treatments
- New model structure address core issues but introduces misalignment with utilities and health states
- "No treatment" arm has 2 health states, "active treatment" arm has 3 health states, incl. partial responders (≥50% to <75%). People in "no treatment" arm may also be a partial responder in the trials (not in model)
- One option is to change response criteria to a 50% reduction in VMS frequency from baseline (if meaningful) – this would mean removal of the "partial responder" health state that causes the mismatch
- Alternatively, could remove the 52-week stopping rule for partial responders as EAGs expert confirmed people are likely to continue on treatment over 1 year with a partial response – EAG base case

Abbreviations: CHMP, Committee for Medicinal Products for Human Use, EMA, European Medicines Agency, VMS, vasomotor symptoms

Key issues: New modelling approach for health states & utilities

EAG: Company active and non-active treatment arms do not align



- How does committee wish to model the active and no treatment arms?

Abbreviations: VMS, vasomotor symptoms

Key issues: Treatment independent utility values

Company response to draft guidance

- No utility data for desvenflaxine or paroxetine. Reasonable to assume greater utility for fezolinetant than desvenflaxine due to improved efficacy so desvenflaxine utility modelled as mean of fezolinetant and no active treatment arms values.

EAG comments

- This is double counting: effect of greater efficacy is already captured in the model
- EAG clinical experts: this isn't plausible → same responder status should mean the same utility so EAG use treatment independent utilities for active treatment arms
- However, not appropriate to use the same utilities for the no active treatment arms because the health states are not the same → You cannot use the same value for a partial responder as a non-responder
- E.g because of misalignment there are different utility values for off treatment in an active treatment arm (0.797) and no active treatment arm (0.792)
- Ideally the model would have been built around three health states in both arms (responder, partial responder or non-responder) with appropriate utilities and probability of response for each group sourced from the trials.
- In absence of this, EAG prefer to use treatment independent utilities for the active treatment arms (see next slide)

Which utility values should be used for the various health states and arms?

Abbreviations: VMS, vasomotor symptoms

Health state utilities used in the model

Company and EAG differ in preferences for partial/responder values (in green)

Treatment	Health-state	Company utility (95%CI)	Source
Fezolinetant	Pre-response assessment**	0.826 (0.812-0.839)	Pooled EQ-5D-5L data in the DAYLIGHT and SKYLIGHT 1 & 2
	Responder	0.837 (0.823-0.852)	
	Partial responder	0.816 (0.800-0.832)	
Desvenlafaxine (or paroxetine scenario)	Pre-response assessment**	0.811	Company: mean change from baseline utility across no active treatment and fezolinetant arms
	Responder	0.826* (EAG 0.837)	
	Partial responder	0.804* (EAG 0.816)	
No active treatment	Pre-response assessment**	0.797 (0.783-0.811)	Pooled EQ-5D-5L data in the DAYLIGHT and SKYLIGHT 1 & 2
	Responder	0.814 (0.797-0.830)	
	Non-responder	0.792 (0.778-0.807)	
No treatment	Off treatment with VMS	0.797 (0.783-0.811)	

EAG use treatment independent values for desvenflaxine: Responder = 0.837, Partial responder = 0.816
** Pre=response assessment conducted at week 12

Which utility values should be used for the various health states and arms?

Abbreviations: VMS, vasomotor symptoms

Key issues: Uncaptured costs of liver monitoring for FEZO

At ACM1

Liver function monitoring is needed

- before treatment + monthly for the first 3 months periodically based on clinician discretion
- when there are symptoms suggestive of liver damage

Web comments

Evidence suggests liver changes resolved on discontinuation, so costs of liver damage unlikely incurred

Week	Responder	Non-responder	Visiting already?
0	0.00	0.00	Yes
4	1.00	0.00	Yes
8	1.00	0.00	Yes
12	1.00	1.00	-
24	1.00	1.00	-
36	1.00	1.00	-

Company submission

GP Omnibus survey responses (n=1,003) estimated average frequency of 43 LFTs per month (current practice)
Included LFTs in the model as was specified in the SmPC: monitored for first 3 months and then additional LFTs in people who have elevated liver enzymes during the first year of treatment (4.42% in DAYLIGHT)

EAG comments

- Company only included additional nurse costs for liver testing in a scenario, not base case.
- EAG considers both costs should be included + annual LFT cost for all → CEs advises annual LFTs for people on FEZO as no long term safety data (as recommended in NG23)

Which approach to including liver monitoring costs is more appropriate?

Abbreviations: CHMP, Committee for Medicinal Products for Human Use, EMA, European Medicines Agency, VMS, vasomotor symptoms

Summary of company and EAG base case assumptions

Assumption	Company base case	EAG base case
Response NMA	Simple random effects primary NMA	Simple random effects sensitivity extended dose NMA
Discontinuation NMA	Simple fixed effects primary NMA	Simple random effects sensitivity extended dose NMA
Stopping rule at Week 52 for partial responders (active treatment arms only)	Included (only responders continue treatment beyond 52 weeks)	No. Partial responders continue on treatment until cycle discontinuation, with a higher per cycle probability of discontinuation compared to responders
Treatment-independent utility values for responders and partial responders	No	Yes, utility values for desvenlafaxine responders and partial responders the same as FEZO responders and partial responders.
Include additional nurse appointments for liver testing	No	Yes

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Abbreviations: EAG, external assessment group; HRT, hormone replacement therapy.

Company base case results

Summary of the company's deterministic and probabilistic base case results (pairwise comparison with fezolinetant)

Deterministic							
	Total			Incremental			ICER
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	(£/QALY)
Fezolinetant	£2,160.52	8.449	6.915	-	-	-	-
No Treatment	£1,675.89	8.449	6.868	£484.63	0.000	0.047	£10,313
Desvenlafaxine	£1,558.51	8.449	6.881	£602.01	0.000	0.034	£17,969
Probabilistic							
Technologies	Total			Incremental			ICER
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	(£/QALY)
Fezolinetant	£2,157.08	8.436	7.088	-	-	-	-
No Treatment	£1,664.31	8.436	7.040	£492.77	0.000	0.048	£10,263
Desvenlafaxine	£1,547.11	8.436	7.054	£609.97	0.000	0.034	£18,053

Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; HRT, hormone replacement therapy; VMS, vasomotor symptoms.

EAG base case results

Summary of the EAG's deterministic and probabilistic base case results (pairwise comparison)

This includes, a simple random effects, extended dose NMA, treatment independent utility, no stopping rule for partial responses (continue until discontinuation) and cost of additional nurse appointments

Deterministic	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, / QALY
Fezolinetant	£2,439.96	6.92	-	-	-
No Treatment	£1,675.89	6.87	£764.08	0.055	£13,977
Desvenlafaxine	£1,572.79	6.89	£867.17	0.031	£28,404
Probabilistic	**Costs**	**QALYs**	**Inc. Costs**	**Inc. QALYs**	**ICER, / QALY**
Fezolinetant	£2,442.24	7.10	-	-	-
No Treatment	£1,669.35	7.05	£772.89	0.055	£13,929
Desvenlafaxine	£1,562.90	7.07	£879.34	0.029	£30,213

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Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; HRT, hormone replacement therapy; VMS, vasomotor symptoms.

EAG scenario analysis

Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, / QALY
Deterministic						
+ Week 52 partial responder stopping rule (as per company base case)	Fezolinetant	£2,170.12	6.91	-	-	-
	No Treatment	£1,675.89	6.87	£494.24	0.047	£10,517
	Desvenlafaxine	£1,556.54	6.89	£613.58	0.026	£23,801
Probabilistic						
+ Week 52 partial responder stopping rule (as per company base case)	Fezolinetant	£2,167.79	7.10	-	-	-
	No Treatment	£1,669.35	7.05	£498.43	0.047	£10,512
	Desvenlafaxine	£1,542.30	7.07	£625.48	0.025	£25,253

Appendix

Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; HRT, hormone replacement therapy; NMA, network meta-analysis; SEE, structured expert elicitation; VMS, vasomotor symptoms.

Fezolinetant for treating vasomotor symptoms associated with the menopause (4)

- ❑ Background, responses to draft guidance and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Other considerations**

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Other considerations

Severity modifier

- Not applied.

Potential uncaptured benefits

- Impact of FEZO on living with VMS including CVD risk associated with unmanaged VMS
- Impact of FEZO on VMS severity (as opposed to frequency)

Managed access

- Not applied – company anticipates routine commissioning.

- Are there any uncaptured benefits?
- How should the equality issues detailed inform the appraisal and are there any other equality issues not already considered?
- What are the uncertainties, and can they be resolved with further data collection?

Fezolinetant for treating vasomotor symptoms associated with the menopause [ID5071]

Supplementary appendix

NICE National Institute for Health and Care Excellence

Key issues: Population

AT ACM1

- Limited treatment options for people with breast cancer but neither HRT nor fezolinetant recommended for people with oestrogen dependent cancer
- SmPC: For oestrogen-dependent cancer: not recommended in women undergoing oncologic treatment. Can be used with individual risk assessment for previous oestrogen cancer post oncologic treatment.

Web responses

- Draft guidance says: FEZO can't be used for people with breast cancer as not licensed for that use but:

→ majority of non-hormonal options in current treatment are not licensed for people with breast cancer; if risks are assessed, could FEZO be considered in the same way?

→ unmet need suggests conditional access could be offered for specific groups while evidence is gathered

- Some prescribed FEZO privately after discussion on risk and experienced a reduction in VMS
- Recommendations are methodologically sound but a more flexible, patient-centred approach to address unmet needs in population could better support the NHS
- HIGHLIGHT-1: FEZO in people with breast/ovarian cancer, HRT unsuitable: could be used when available.

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- Acknowledges that some medications are used off licence for this indication, but committee can only recommend within the marketing authorisation (further information on MHRA recommended population).

Abbreviations: HRT, hormone replacement therapy; FEZO, fezolinetant; ; NMA, network meta-analysis; SmPC, summary of profuct characteristics (regulatory document from MHRA); VMS, vasomotor symptoms

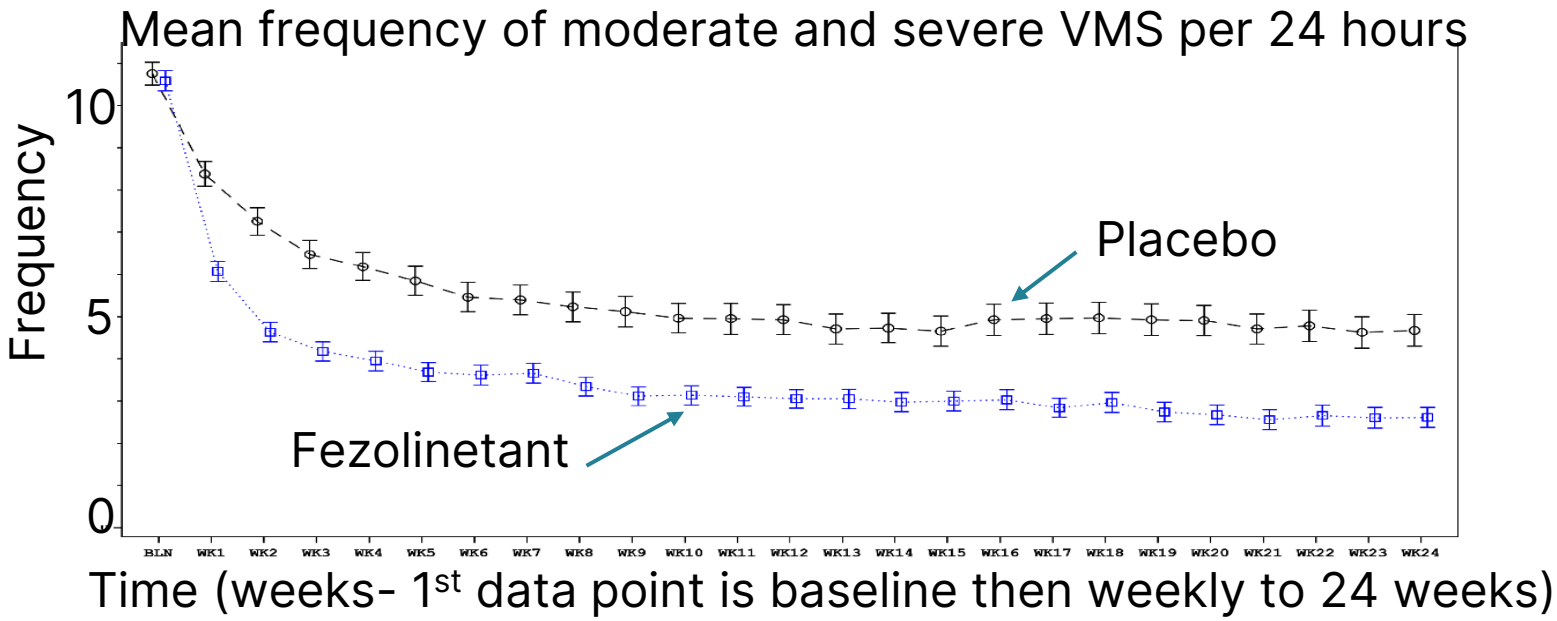
Key clinical trials

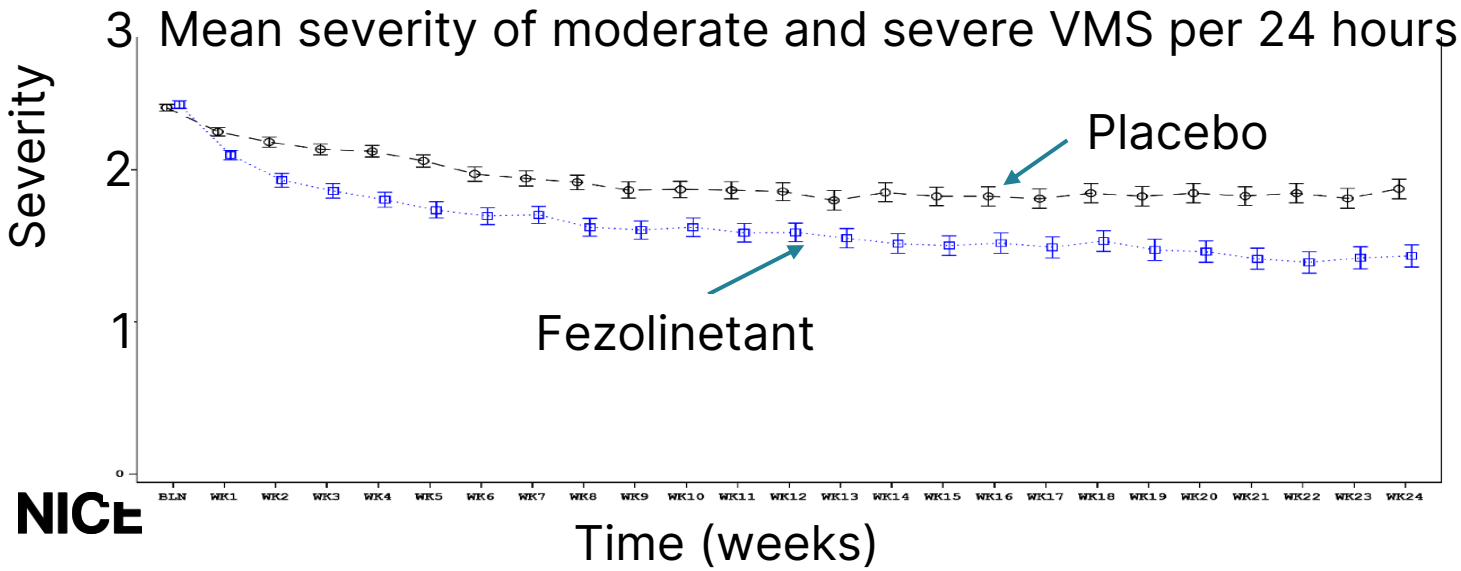
* See appendix - How severity defined in trial

	DAYLIGHT	SKYLIGHT 1/2 (identical designs)
Population	Menopausal people aged 40 to 65 years with moderate to severe VMS & deemed **unsuitable for HRT**	Menopausal people aged 40 to 65 years with moderate to severe VMS
Key eligibility criteria	Minimum average of 7 moderate to severe events of VMS/day in last 10 days prior to randomisation	Minimum average of 7 to 8 moderate to severe VMS/day, or 50 to 60/ week in last 10 days prior to randomisation
Comparison	Fezolinetant 45 mg vs placebo	Fezolinetant 45 mg or 30 mg vs placebo
Duration	24 weeks	12 weeks, plus a 40-week double-blind uncontrolled extension period
Primary outcome	Mean change in VMS frequency, from baseline to week 24	Mean change in VMS frequency and severity from baseline to weeks 4 and 12
Used in model?	Yes, including EQ-5D-5L	Data from HRT-unsuitable pre-specified subgroup who had 45mg dose of fezolinetant

Abbreviations: EQ-5D-5L, European Quality of Life 5 Dimensions 5 Level Version; HRT, hormone replacement therapy; VMS, vasomotor symptoms

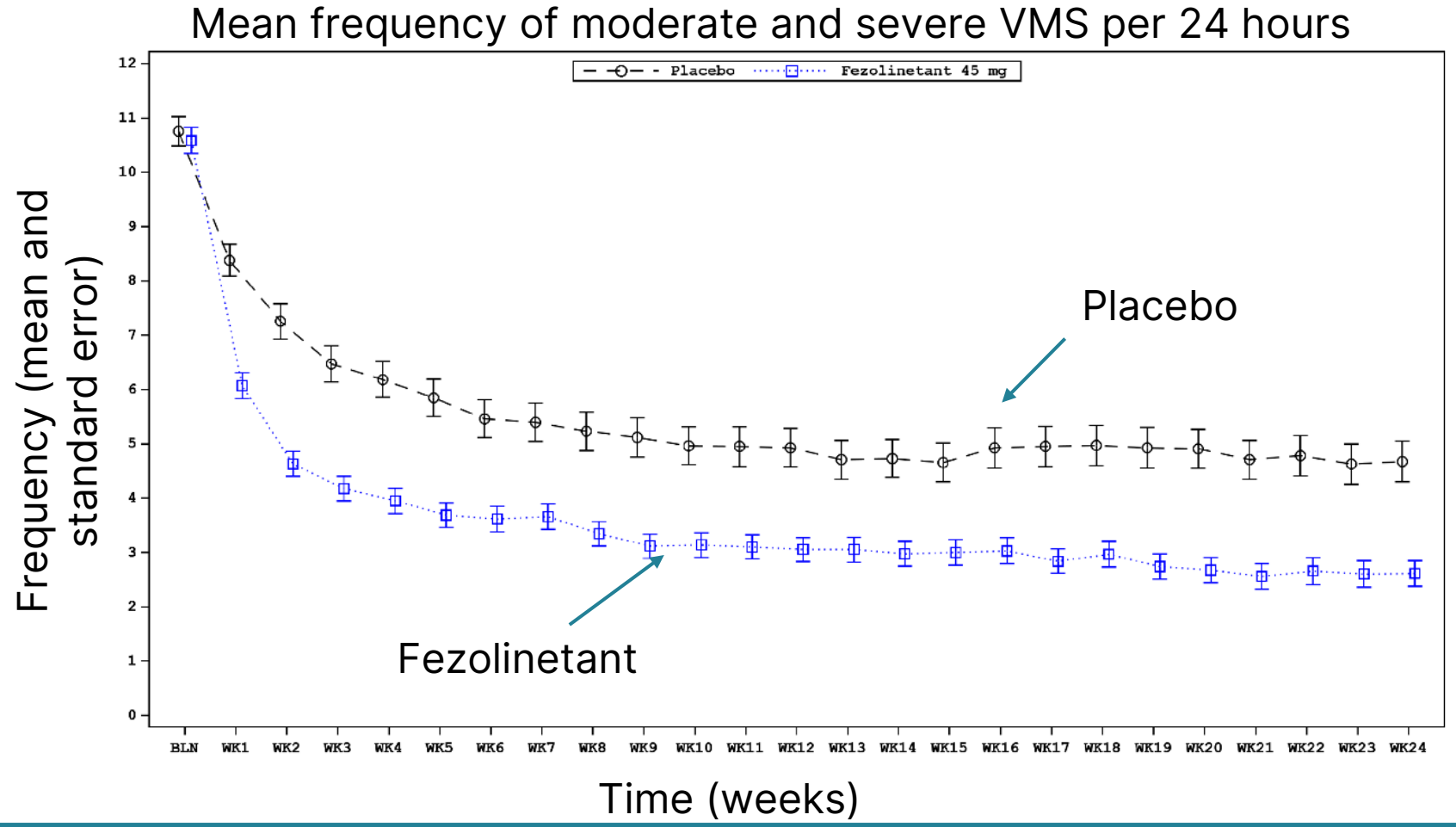
Key clinical trial results- summary





- DAYLIGHT (data in graphs) and SKYLIGHT (pooled) showed a statistically significant reduction in VMS frequency and severity
- EAG presented responder analysis for ≥50%, ≥75%, and 100% reduction in VMS frequency showing higher proportion of responders with fezolinetant in each category→ not in model but less at risk of bias due to missing data assumptions than continuous data

Key clinical trial results (DAYLIGHT) – VMS frequency

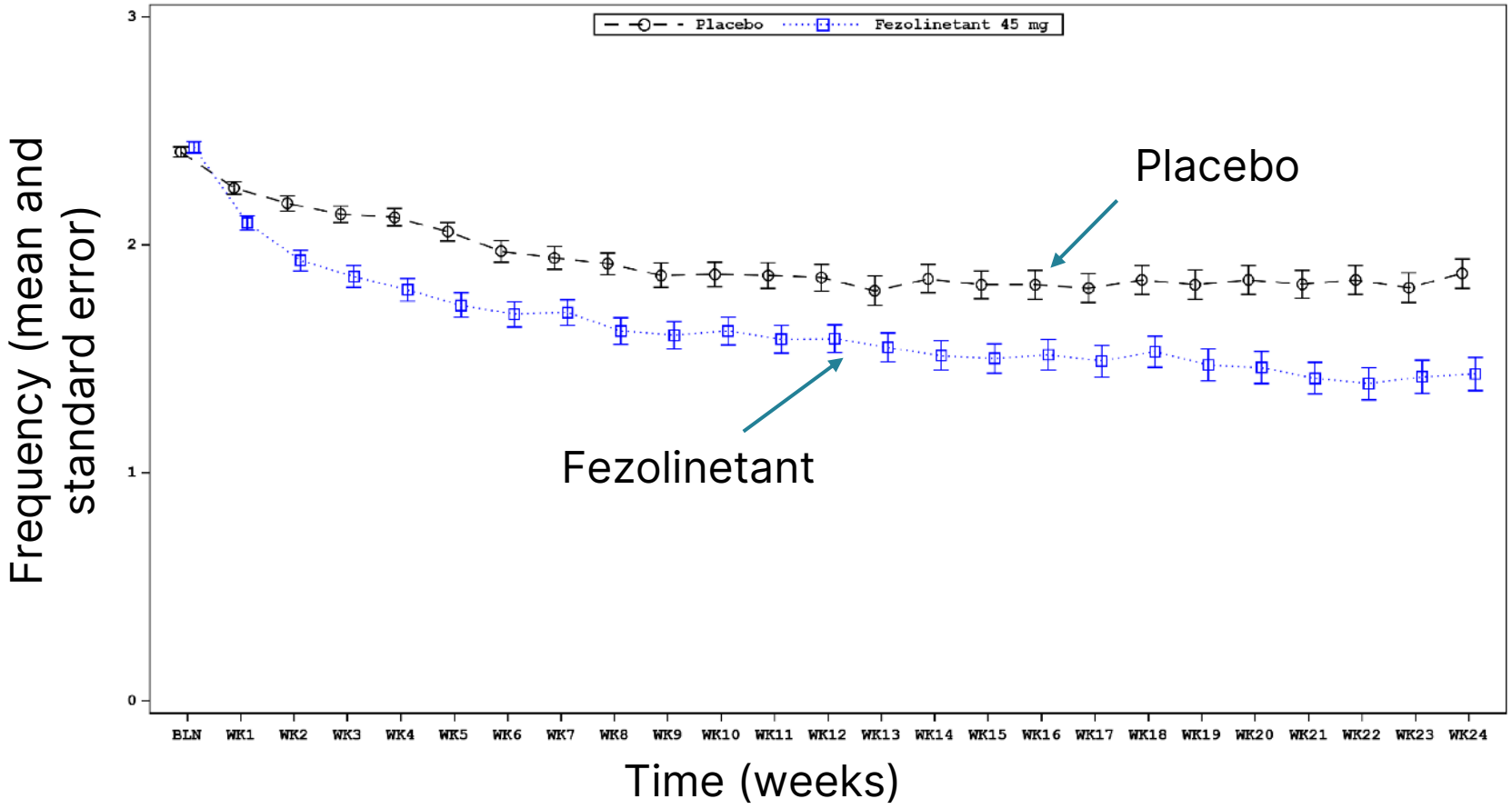


Difference in LS Means: fezolinetant versus placebo	
LS mean (SE)	−1.93 (0.36)
p value	<0.001

Abbreviations: LS, least squares; SE, standard error; VMS, vasomotor symptoms.

Key clinical trial results (DAYLIGHT) – VMS severity

Mean severity of moderate and severe VMS per 24 hours



Difference in LS Means: fezolinetant versus placebo	
LS mean (SE)	−0.39 (0.09)
p value	<0.001

Return to clinical effectiveness section

Abbreviations: LS, least squares; SE, standard error; VMS, vasomotor symptoms.

Key clinical trials – VMS frequency (responder analyses)

Trial	Responders with ≥ 50% Reduction		Responders with ≥ 75% Reduction		Responders with 100% Reduction	
	Fez 45mg	Placebo	Fez 45mg	Placebo	Fez 45mg	Placebo
DAYLIGHT Week 24	[redacted]		[redacted]		[redacted]	
OR (95% CI)	[redacted]		[redacted]		[redacted]	
DAYLIGHT Week 12	[redacted]		[redacted]		[redacted]	
OR (95% CI)	[redacted]		[redacted]		[redacted]	
SKYLIGHT 1 Week 12	[redacted]		35%*	13%*	[redacted]	
OR (95% CI)	3.16 (2.04 to 4.94)		NR		3.26 (1.33 to 9.19)	
SKYLIGHT 2 Week 12	[redacted]		[redacted]		[redacted]	
OR (95% CI)	[redacted]		[redacted]		[redacted] NMA	

Return to clinical effectiveness section

Abbreviations: CI, confidence intervals; OR, odds ratio; NR, not reported VMS, vasomotor symptoms.

Key clinical trials - discontinuation

Return to main presentation

Trial discontinuations and missing data at primary endpoints in the key clinical trials

Trial	Proportion of patients who discontinued trial intervention		Proportion of patients with missing data at primary endpoints	
	Fezolinetant	Placebo	Fezolinetant	Placebo
DAYLIGHT	14%, 5% due to TEAE	23%, 6% due to TEAE	22%	27%
SKYLIGHT 1	8%, 3% due to TEAE	13%, 5% due to TEAE	16%	21%
SKYLIGHT 2	7%, 1% due to TEAE	10%, 1% due to TEAE	13%	16%

In the model For fezolinetant, the per cycle probability of discontinuation of 2.43% was derived from week 0–24 DAYLIGHT data and applied in each model cycle up to week 24. From week 24 onwards, the per cycle probability of discontinuation of [redacted] was sourced from pooled SKYLIGHT 1 and 2 week 24–52 trial data (HRT-unsuitable). This resulted in a median treatment duration with fezolinetant of [redacted] years

Abbreviations: TEAE, treatment-emergent adverse event